## P030047 Lead Reviewer Memo

**History/Background/Overview**

The Cordis PRECISE Nitinol Stent and the Angioguard XP Emboli Capture Device have been under clinical investigation since 1998. There have been many modifications made to the device design, the materials of construction, the sizes and configurations to be offered, and even the name of the device. When the study was first proposed, the device was called the S.M.A.R.T. stent, but the name changed when the profile was modified. The most significant changes have been the addition of the Angioguard as part of the pivotal study, the lowering of the device profile, and the recent transition from an over-the-wire technology to a rapid exchange design.

In the clinical section, all stent designs have been pooled, and analyses presented to justify such pooling. The sponsor tested each design on the bench, and some changes were also validated in an animal model. There was no clinical use of the rapid exchange configuration, but FDA agreed to consider marketing clearance of the rapid exchange technology without clinical testing since the working ends (the filter and the stent) have not been changed.

Initially, the sponsor proposed a randomized study, with registry arms for stenting and surgery for patients whom the surgeon, interventionalist and neurologist all agreed could not be randomized. Correction/clarification: the surgeon, interventionalist, and neurologist team determined if patients met entry criteria; the team did not determine if a patient was entered into the registry. Entry into stent registry occurred if the surgeon felt a patient was too high-risk for surgery. Entry into CEA registry occurred if the interventionalist felt a patient was inappropriate for stenting. This design is outlined in SAPPHIRE protocol and report, and was clarified during a telephone call to Cordis from FDA on March 22, 2004 (B. Zuckerman to J. Martin). The sponsor was unable to complete the randomized study, mostly due to competing studies, and because the stent registry arm filled up (i.e., physicians were no longer willing to randomize patients). Some of these competing studies involved competitor devices, but many involved the Cordis devices. While Cordis did not monitor, fund or sponsor these single-investigator studies, they were facilitated by Cordis. For the most part, these single investigators used the Cordis-supplied feasibility (non-randomized) protocol drafted by Cordis, and the Cordis case report forms and consent form, to do their studies. (In order to open a study, each investigator-sponsor needed a letter of authorization from Cordis to cross reference the Cordis file for the manufacturing information and non-clinical testing). Some of these single investigators opened their own studies after being investigators in the Cordis trial, and others did not participate in the Cordis trial. Cordis has asked that we clarify this memo to state that the study was stopped due to slow enrollment, which was considered an administrative reason. Furthermore, they asked that we state that "Although there were competitor trials, none involved Cordis devices. SAPPHIRE centers did not initiate their investigator-sponsored IDE studies until enrollment in SAPPHIRE was complete." However, this is not FDA' s perception of the situation; we stand by our initial statements on this issue.

The PMA is a compilation of data from the Cordis-sponsored IDE (consisting of data from the 261 patient feasibility non-randomized study, the 334 patient randomized pivotal study, the 406 patients enrolled into the stent registry arm and the 7 patients enrolled into the surgical registry

arm), and most (but not all) of the single-investigator IDEs, as well as data from non-U.S. Cordis-sponsored study (CASCADE). The CASCADE and the single-investigator studies only include 30-day data, whereas the feasibility and SAPPHIRE studies have data to beyond one year. The table on page 4 of this memo summarizes the data from each study, so you can see it at a glance. Although the sponsor updated their rate table in an amendment to the PMA, they only included data for patients having 2 year case report forms; those with events who did not have a 2-year report form were omitted from the tables. These tables were omitted from the Panel Pack, as they were incomplete. The survival curves were left in, however.

In addition after the Panel Pack was submitted, but prior to mailing it out, the sponsor provided more details regarding the reasons for entering patients into the registry group rather than the randomized cohort, details about patients who were adjudicated in or out, and detailed reasons why the randomized study was terminated, which are in the Panel Pack, under the section labeled "Addendum".

There were several people on the review team who helped to review information in this PMA, including the following:

- ?? Lead Clinical Reviewer Dr. Ronald Weintraub,
- ?? Additional clinical oversight from Drs. Paul Chandeysson and Wolf Sapirstein
- ?? Statistical reviewer Heng Li
- ?? Engineering reviewers Deanna Busick, Vivianne Holt, and Terry Woods
- ?? Microbiological, biocompatibility and animal reviewer Lisa Kennell
- ?? Many others have reviewed the patient labeling, manufacturing, and oversaw inspections of the company and some of the hospital source data.

Based on input and reviews performed to date of the non-clinical information in the file, there are a few minor remaining questions that must be resolved relating to the non-clinical data. The sponsor did not agree with this statement as FDA had not indicated that there were issues remaining. The phrasing should have been that the FDA continues to review some aspects of the non-clinical information as of this writing. Substantive reviews of these data are not included in the submission, but the sponsor's summary provided in the Summary of Safety and Effectiveness provides adequate detail for your needs. If you are interested in having a copy of the complete reviews from the FDA team member, they can be provided upon request.

Regarding issues pending from the clinical and statistical reviews, a few issues remain and the sponsor's response is pending. Some of the clinical concerns have been included for discussion at the Panel meeting as questions to the panel.

Outstanding issues as of this writing include the following:

1. The sponsor has been asked to perform an observational study using a propensity score analysis of the randomized patients and the stent registry. As of this writing, this analysis has not been done. The sponsor disagreed with this statement, and in fact it is incorrect and should have been updated. Cordis had submitted a propensity score analysis, but it may not have been optimized with regard to the covariates

chosen. If it is submitted, the results will be forwarded to you as an amendment to this Panel Pack. The summary of the results were, in fact, included in the Panel Pack, under the tab labeled "ADDENDUM." The sponsor was asked to provide detailed computational steps for the confidence interval used for the claim of non-inferiority, which is based on the parameter ? (theta) and a confidence interval for this parameter. Correction: this information was provided to the statistician.

2. The statistician asked for the baseline data for patients offered the option of entering CEA registry but who did not enter, and those offered the option of the stent registry who did not enter. Again, I neglected to update this memo; the sponsor responded that they were not aware of patients in this category.

3. We asked for more details about the events that were discrepant between the sites and the CEC (i.e. events that were either added in or adjudicated out). This information arrived late, and was added at the end of the FDA review memos under the tab labeled "ADDENDUM.".

**Device Description**

The PRECISE is a self-expanding nitinol stent, available in 5.5F and 6F delivery systems. The geometry of the stent struts can be described as a fine ziz-zag mesh. The stent is laser-cut from nitinol tubing into zig-zag rings, with links between the rings. The 5.5F stent is cut from 0.060" OD tubing, and the 6F stent is cut from 0.072" OD tubing. All stent sizes within each family are cut using the same pattern and dimensions; final stent size is achieved by expanding the stent on an appropriately sized mandrel and heat-treating it to set its shape. Stent length is determined by the number of zig-zag rings; longer stents have more rings.

The 5.5F PRECISE stent is available in straight sizes of 5, 6, 7, and 8 mm diameter, each with available lengths of 20, 30, and 40 mm. A tapered version is also available, measuring 6-8 mm in diameter and 30 mm in length.

The 6F PRECISE stent is available in straight sizes of 9 and 10 mm diameter, each with available lengths of 20, 30, and 40 mm. Two tapered versions are also available, measuring 7-9 and 7-10 mm in diameter and 30 mm in length.

The Angioguard XP is a 0.014" guidewire with a filter basket near the distal end. It functions as both an interventional guidewire and a distal embolic protection device during carotid procedures. The filter basket consists of a thin, porous membrane supported by a nitinol skeleton and is designed to trap and capture emboli. After the filter (inside a deployment sheath) is advanced to the proper position within the vessel, the deployment sheath is removed from the guidewire. The filter basket opens like an umbrella, and the guidewire is used to facilitate positioning of other interventional devices (e.g., stents or balloons). When the interventional procedure is complete, a capture sheath is advanced over the wire to close the filter by collapsing the proximal struts of the basket (the actual filter element is not captured inside the sheath). The capture sheath is locked to the guidewire, and the entire assembly is withdrawn from the patient.

The ANGIOGUARD XP is available in two wire stiffnesses: Medium Support and Extra Support. Both are available in filter basket sizes of 4, 5, 6, 7, and 8 mm diameter and 300 mm length. The Extra Support version is also available in a 180 mm length. The sponsor provided

clarification/revisions to the original spreadsheet created by FDA. The sponsor stated the following: "The FDA's spreadsheet provided a summary of all studies included in Cordis' PMA; however, in some areas, the data differed from what Cordis presented. In the ITT columns, FDA changed the denominator to 167 for lesion success, procedure success, stent success, and ANGIOGUARD success. For these variables, Cordis utilized considered "Attempt to treat" to accurately assess the performance of the stent and ANGIOGUARD devices. Device performance cannot be assessed if it is not attempted. For all other variables, the strict intent-to-treat definition was utilized. In addition, Feasibility Study data were presented as "Without ANGIOGUARD". The Feasibility Study was conducted both with and without ANGIOGUARD (as reported in the clinical report). Therefore, Cordis modified the table to indicate combined results, results without ANGIOGUARD, and results with ANGIOGUARD. Also, in the Site-Sponsored Studies, TLR data were not available, but TVR data were. We corrected that section accordingly. We also added in the "N" for the investigator- sponsored studies in the heading.

Also, Cordis is not clear whether the data FDA entered in the table for "Death/Ipsilateral Stroke" represents a combination of death and ipsilateral stroke, or death due to ipsilateral stroke. As well, we are not clear on how these data were determined."

Safety and Effectiveness Measures to One Year (unless noted)

| Parameter | Randomized Pivotal Study | | | | Stent Registry (N=406) |
|---|---|---|---|---|---|
| | ITT Stent (N=167) | Evaluable Stent (N=159) | ITT CEA (N=167) | Evaluable CEA (N=151) | |
| **Safety Measures** | | | | | |
| MAE (30 day death, stroke, MI, and death and ipsilateral stroke >30 days to 12 months) | 12.0% (20/167) | 11.9% (19/159) | 19.2% (32/167) | 19.9% (30/151) | 15.8% (64/406) |
| MAE (without non-neurologic deaths 31-360 days) | 6.0% (10/167) | 5.7% (9/159) | 12.6% (21/167) | 12.6% (19/151) | 10.3% (42/406) |
| MAE (without MIs to 30 days and without non-neurologic death 31-360 days) | 5.4% (9/167) | 5.0% (8/159) | 7.8% (13/167) | 7.3% (11/151) | 9.4% (38/406) |
| Death/ipsilateral stroke | 11.4% (19/167) | 10.7% (17/159) | 17.4% (29/167) | 17.9% (27/151) | 17.2% (70/406) |
| Death | 7.2% (12/167) | 6.9% (11/159) | 12.6% (21/167) | 12.6% (19/151) | 10.1% (41/406) |
| Any stroke/TIA | 12.6% (21/167) | 12.6% (20/159) | 10.2% (17/167) | 10.6% (16/151) | 16.0% (65/406) |
| Stroke<br>Major ipsilateral<br>Minor ipsilateral<br>Non-ipsilateral | 6.6% (11/167)<br>0.6% (1/167)<br>3.6% (6/167)<br>3.6% (4/167) | 5.7% (9/159)<br>0% (0/159)<br>3.8% (6/159)<br>2.5% (4/159) | 3.4% (14/167)<br>3.0% (5/167)<br>1.8% (3/167)<br>3.6% (6/167) | 7.3% (11/151)<br>3.3% (5/151)<br>2.0% (3/151)<br>2.6% (4/151) | 9.1% (37/406)<br>3.2% (13/406)<br>3.9% (16/406)<br>2.2% (9/406) |
| TIA | 6.6% (11/167) | 6.9% (11/159) | 3.0% (5/167) | 3.3% (5/151) | 6.9% (28/406) |
| MI<br>Q wave<br>Non-Q-wave | 3.0% (5/167)<br>0% (o/167)<br>3.0% (5/167) | 2.5% (4/159)<br>0% (0/159)<br>2.5% (4/159) | 7.2% (12/167)<br>1.2% (2/167)<br>6.0% (10/167) | 7.9% (12/151)<br>1.3% (2/151)<br>6.6% (10/151) | 2.7% (11/406)<br>0.5% (2/406)<br>2.2% (9/406) |
| **Effectiveness Measures** | | | | | |
| Lesion success (residual stenosis <30%) | 98.1% (145/158) | 91.8% (145/158) | N/A | N/A | 90.4% (368/407) |
| Procedure success | 88.1% (140/159) | 88.6% (140/158) | N/A | N/A | 87.9% (355/404) |
| Device (stent) success | 91.2% (145/159) | 91.2% (145/159) | N/A | N/A | 89.6% 363/405) |
| Angioguard success | 95.6% (152/159) | 95.6% (152/159) | N/A | N/A | 91.6% (372/406) |
| Presence of trapped material | | | N/A | N/A | 56.0% (220/393) |
| Target Lesion Revascularization<br>Surgery<br>PTA | 0.6% (1/167)<br>0.6% (1/167)<br>0% (0/167) | 0.6% (1/159)<br>0.6% (1/159)<br>0% (0/159) | 3.6% (6/167)<br>0.6% (1/167)<br>3.0% (5/167) | 4.0% (6/151)<br>0.7% (1/151)<br>3.3% (5/151) | 0.7% (3/406)<br>0% (0/406)<br>0.7% (3/406) |
| Target Vessel Revascularization<br>Surgery<br>PTA | 0% (0/167)<br>0% (0/167)<br>0% (0/167) | 0% (0/159)<br>0% (0/159)<br>0% (0/159) | 0% (0/167)<br>0% (0/167)<br>0% (0/167) | 0% (0/151)<br>0% (0/151)<br>0% (0/151) | 0% |
| Stent thrombosis | 0% (0/167) | 0% (0/159) | | | 0.7% (3/406) |
| Major bleeding | 9.0% (15/167) | 9.4% (15/159) | 10.2% (17/167) | 11.3% (17/151) | 13.3% (54/406) |
| Severe hypotension | 17.4% (29/167) | 18.2% (29/159) | 3.0% (5/167) | 3.3% (5/151) | 15.5% (63/406) |
| Bradycardia/asystole | 8.4% (14/167) | 8.8% (14/159) | 3.0% (5/167) | 2.6% (4/151) | 3.4% (14/406) |
| Cranial nerve injury | 0% (0/167) | 0% (0/159) | 4.8% (8/167) | 5.3% (8/151) | 0% (0/406) |

| Feasibility Study | | | Investigator-Sponsor Studies (non-adjudicated, **30 day only**) (N=490) | CASCADE OUS Study **(30 day only)** | |
|---|---|---|---|---|---|
| Feasibility Study Total (N=261) | **Without Angioguard (N=176)** | **With Angioguard (N=85)** | | **Without Angioguard** (N=90) | With Angioguard (N=31) |
| **Safety Measures** | | | | | |
| 10.7% (28/261) | 12.5% (22/176) | 7.1% (6/85) | 4.3% (21/490) | | |
| | | | | | |
| | | | | | |
| % (/261) | | | | | |
| 3.8% (10/261) | 4.0% (7/176) | 3.5% (3/85) | 0.6% (3/490) | 0% (0/90) | 0% (0/31) |
| 14.6% (38/261) | | | | 18.9% (17/90) | 3.2% (1/31) |
| 8.4% (22/261)<br>1.5% (4/261)<br>5.5% (14/261)<br>1.5% (4/261) | 2.3% (4/176)<br>6.3% (11/176) | 0% (0/85)<br>3.5% (3/85) | 2.6 (13/490) | 10% (9/90)<br>2% (2/90)<br>6% (6/90)<br>1.1% (1/90) | 3.2% (1/31)<br>0% (0/31)<br>3% (1/31)<br>0% (0/31) |
| 6.1% (16/261) | | | 1.6% (8/490) | 8.9% (8/90, 7 ipsilateral) | 0 (0/31) |
| 1.5% (4/261)<br>0% (0/261)<br>1.5% (4/261) | | | 1.4% (7/490)<br>0.2% (1/490)<br>1.2% (6/490) | | |
| **Effectiveness Measures** | | | | | |
| 95.8% (249/260) | 96.6% (170/176) | 94.0% (79/84) | 94.7% (414/437) | | |
| 90.4% (235/260) | 89.8% (158/176) | 91.7% (77/84) | 93.8% (408/435) | | |
| 92.3% (240/260) | 94.3% (166/176) | 88.1% (74/84) | 94.3% (410/435) | | |
| 86.7% (78/90) | N/A | 86.7% (78/90) | 95.7% (440/460) | | |
| 53.8% (42/78) | N/A | 58.3% (42/78) | | | |
| 98.5% free from TLR<br>1.1% (3/261)<br>0.4% (1/261) | 97.5% Free from TLR | 100% Free from TLR | | | |
| 0% (0/261)<br>0% (0/261)<br>0% 0/261) | 0% (0/176)<br>0% (0/176)<br>0% (0/176) | 0% (0/85)<br>0% (0/85)<br>0% (0/85) | 0.2% (1/490) (30-day rate) | | |
| 0.4% (1/261) | | | 0.6% (3/490) | | |
| 6.5% (17/261) | 8.0% (14/176) | 3.5% (3/85) | 2.4% (12/490) | | |
| 10.7% (28/261) | | | 10.4% (51/490) | | |
| 3.8% (10/261) | | | Not given | | |
| 0% (0/261) | 0% (0/176) | 0% (0/85) | Not given | | |

## Clinical Review, Ronald M. Weintraub, M.D.

**Patient Population:**

Eligible patients classified as "high risk" on the basis of anatomic and/or clinical neurologic criteria.

Anatomic: >80% atherosclerotic stenosis of the common or internal carotid artery by ultrasound or angiogram

Neurologic/clinical: One or more TIAs, or one or more completed strokes, together with a >50% of the internal or common carotid artery

Both symptomatic and asymptomatic patients must also have had one or more characteristics or comorbid conditions that were considered to place them at high risk for carotid endarterectomy (CEA): CHF, cardiac surgery within 6 weeks, recent MI, synchronous carotid and coronary artery disease (CAD) requiring intervention, severe pulmonary disease, contralateral carotid occlusion, contralateral laryngeal palsy, recurrent post-CEA stenosis, post irradiation, abnormal stress test, among others.

Exclusionary Criteria included anatomic inaccessibility, reference segmental diameter <4mm or other anatomic contraindications, acute neurologic ischemia or stroke within previous 24 hours, pertinent allergies, history of coagulopathy.

**Study Design:**

*Prospective, multi-center, randomized group sequential study by Intention-to-Treat (ITT)*

- Open, operative carotid endarterectomy
- Carotid angioplasty and application of Cordis PRECISE™ or PRECISE™ RX Nitinol Stent System, with distal protection system

*Non-Randomized Registry*

- A registry included those patients who met the inclusion criteria but were determined by the surgeon, interventionalist, and neurologist at each study site to be at too high a risk for carotid endarterectomy and therefore inappropriate for randomization. Again, the same clarification is needed here. The surgeon, interventionalist, and neurologist team determined if patients met entry criteria; the team did not determine if a patient was entered into the registry. Entry into stent registry occurred if the surgeon felt a patient was too high-risk for surgery. Entry into CEA registry occurred if the interventionalist felt a patient was inappropriate for stenting. This design is outlined in SAPPHIRE protocol and report, and was clarified during a telephone call to Cordis from FDA on March 22, 2004 (B. Zuckerman to J. Martin).

**Primary Endpoints and Sample Size:**

Primary Safety endpoint is a composite of major adverse events (MAE) including death, any stroke, and/or myocardial infarction at 30 days post procedure, and death and/or ipsilateral stroke between 30 (the sponsor corrected this to be 31 days) days and 12 months post-procedure.

Measure of Treatment Effectiveness: Safety and efficacy of the stent system arm is determined by its superiority or non-inferiority compared with the CEA arm. The 30-day MAE event rate for high-risk CEA was estimated from previous CEA v.medical management randomized trials (ACAS, NASCET, ECST) to be between 6% and 12%.

Sample Size (Intention-to-Treat, i.e., all randomized consented subjects)

- CEA Arm: 167 patients
- Stent Arm: 167 Patients
- Stent Registry: 406 patients
- CEA Registry: 7 patients

Sample size ("Evaluable" Patients, i.e. randomized subjects who actually received treatment to which they were randomized)

- CEA Arm: 151 patients
- Stent Arm: 159 patients

Number of Centers: 29 American (USA) study centers

**Major Secondary Endpoints**

Secondary Safety endpoints include:

- Successful stent deployment
- Successful filter deployment
- Endovascular access complications
- Surgical site complications
- Patency (<50% stenosis) by ultrasound (US) within 48 hours, and 6, 12, 24 and 36 months post procedure
- Independent neurologic assessment at the same time intervals as above
- Composite MAE at the same time intervals

## Analysis of Results

Analysis was performed two ways: using an intent to treat (ITT) and an "evaluable" basis for the denominator. The ITT group consisted of all consented and randomized subjects, whereas the "evaluable" group had a subset of those who included only subjects who actually received the treatment in which they were randomized.

**Patient Characteristics**

"Evaluable" patients or patients withdrawn for reasons other than not receiving randomized treatment

There were 24 of 334 patients that were randomized but never received therapy. Of these, 16 had been randomized to CEA, and 8 to stent. One patient who suffered acute hypertension and

stroke during arterial puncture and whose procedure was terminated before stent insertion, though not included in the "randomized evaluable" patients, was appropriately reported as a MAE (death) in the larger 167-patient ITT arm. Twenty-one patients were withdrawn after randomization, either because of patient request or failure to fulfill I/E criteria upon review.

The following patients might arguably have been reported as MAEs in an ITT series:

Pt # 4, suffered a stroke after randomization to stent upon admission to hospital.
Pt # 10, was randomized to CEA, not performed. Although referred then for stent, pt. died 3 days later, before stent could be implanted.

The sponsor clarified that these subjects were, in fact, included in the ITT analysis; therefore, FDA rescinds this statement.

Patient Characteristics and Comorbid conditions

Patients randomized by ITT to either CEA or Stent were compared by patient characteristics and comorbid conditions: demographics, medical history, risk factors, Charlson Comorbidity Index, and high risk characteristics. These comparisons were made between the arms of the entire cohort (167 v. 167), and also between those of each arm that were considered "symptomatic" (50 stent v. 46 CEA). Only one comparison (2 high risk characteristics, within the symptomatic patients) reached statistical significance ($p = 0.04$): CEA: 23.8% v. stent: 8.0%.

Baseline Carotid Artery Characteristics

Baseline, procedural, and post-procedure angiographic characteristics of the stent cohort are described in several Tables (7-9, pp2-179-181, Vol.2), but I could not find equivalent baseline descriptors in the CEA cohort. The sponsor clarified that CEA patients did not undergo angiography as this is not normal practice for this surgical procedure. Therefore, no such data was collected and reported. FDA amends this language as follows: The CEA preoperative angiography results were not obvious, and there were no early CEA postoperative ultrasound data.

**Results: Primary Endpoints**

Cumulative Percentage of MAE at 30 days (ITT Group):
Stent arm: 8/167, 4.8 % +/- 1.7%
CEA arm: 16/167, 9.8% +/- 2.4%

Eliminating 14 of the 16 patients randomized but withdrawn from treatment (See above), would yield:
For the stent arm: 9/152, 5.9%
For the CEA arm: 17/146, 11.7%

Cumulative Percentage of MAE at 360 Days Among **Evaluable** Patients
Censoring MAE events as adjudicated by the Independent Clinical Events Committee reveals a statistical difference between the two groups: The event rate for Stent is 12.2% +/- 2.6%. That for CEA is 20.1% +/- 3.4%. The curves diverge (Figure 9, PMA Vol 2, p 2-382), and

P=0.048 (Log-Rank), and p=0.045 (Wilcoxon).

Non-Inferiority at 360 Days (ITT Group):

MAE (Death, MI, Stroke): Stent Arm: 20/167, 12.0% CEA Arm: 32/167, 19.2%
Difference: (95% C.I): -7.2% (-14.9%, 0.6%)
Theta: 0.50764 95% C.I. (-0.03620, 1.05149)

**Major Secondary Endpoints**

Failure of Stent or Filter Delivery

There were eight patients in whom failure of stent delivery was encountered. Although seven of these patients ultimately had successful stent delivery at the index procedure, one required CEA. There were 8 additional patients in whom difficulty was encountered in either passing or retrieving the angioguard protection device. Among these 16 patients, 7 were found to have 50-70% stenoses either immediately post-procedure, or by US at the first re-evaluation.

Endovascular Access or Surgical Site Complications

These were few in number in both stent and CEA arms. These are not described in detail.

Stent access site complications: 2 major vascular requiring intervention, 6 hematomas, 4 pseudoaneurysms, 1 A-V fistula, 1 infection for a total complication rate of 8%.

CEA surgical site complications: 1 major vascular, 3 hematomas, 7 cranial nerve injuries (usually hypoglossal), 1 infection, for a total complication rate of 7%.

Patency by Ultrasound at 48 hours, and 6, 12, 24, and 36 months

Post-procedure residual stenosis or restenosis, as measured by peak velocity (PSV) and end diastolic velocity (EDV) showed no difference between the treatment arms. At 6 months, however, both PSV and EDV were higher in the CEA arm (p=0.03 and 0.01, respectively). At one year PSV was still higher in the CEA group (p=0.03), though the difference in PDV did not reach statistical significance. Two and three-year results are not included in the original PMA.

Neurologic follow-up at one year

Of 26 patients not seen for follow-up at one year, 4 had expired, 11 had withdrawn or refused follow-up, 3 were too ill to return and 6 were lost to follow up. Review of the Excel spread sheets shows generally good compliance.

## Review of Deficiencies (amendments to the PMA)

**Significant Deficiency**

*FDA Question: For demonstration of reasonable assurance of safety and efficacy, it is critical to show a sustained benefit (> one year) of your device. In fact, your protocol stipulates...that patients will be followed for three years. A substantial number of patients from your feasibility study, randomized trial, high-risk registry, and OUS CASCADE study are presently beyond the one-year time point. Therefore, please provide detailed longer-term data (> one year) for these cohorts in order to demonstrate sustained safety and efficacy.*

Summary of response: Of the 121 patients entered into the CASCADE study, 68 were followed for 12 months. The sponsor states that four further strokes occurred between the one and 6-month intervals. There were no further TIAs. There were two other deaths, not considered device-related, that occurred during this interval. The sponsor states that there were no further strokes between 6 and 12 months. Neurologic examinations were not complete. There were 112 performed at discharge, 94 at one month, 98 at six months, and 68 at one year. The sponsor states that "No further follow-up was required for the CASCADE study".

The sponsor supplied MAE data for those patients in the randomized stent and CEA arms of the SAPPHIRE trial followed for two years, for the SAPPHIRE stent registry to two years, and the feasibility study out to three years.

For the SAPPHIRE randomized arms, 2-year data are presented in two ways. In the first, if an event (even death) occurred in a patient without a 2-year contact, it did not appear in the rate table. In the other, since events may have been recorded on patients that did not have a 2-year contact, the sponsor provided data on the entire patient populations. For the randomized arms, the MAE rates are 19.2% (stent) v. 26.7% (CEA), and death rates are 14.4% (stent) v. 20.9% (CEA). The differences did not reach statistical difference.

Similarly, for the SAPPHIRE randomized arms, cumulative ipsilateral stroke rates at 2 years were 5.9% (stent) v. 5.8% (CEA), and the MI rates were 6.0% (stent) v. 8.7% (CEA), with no statistical difference between groups.

With respect to restenosis at 2 years (for those patients having US studies), the stent restenosis rate was 13/75=17.3% v. 6/45=13.3% for CEA (p=NS).

In the SAPPHIRE Stent Registry, the cumulative MAE rate was 26.4% at two years.

The restenosis rate among those patients examined at two years was 47/138, or 34.1%.

For the feasibility study patients followed for three years, the MAE rate was 21.8% and 13.9%, depending on the method of calculation (see above). The sponsor was confused by these numbers. In fact, upon re-review, these represent MAE and death, respectively, at 1080 days.

2 Year Adverse Events Rates

| STUDY ARM | MAE | IPSILAT STROKE | RESTENOSIS |
|---|---|---|---|
| **RANDOM STENT** | 19.2% | 5.9% | 38.7% (IVS) |
| **RANDOM CEA** | 26.7% | 5.8% | 26.6% (IVS) |
| **REGISTRY STENT** | 26.4% | 9.3% | 34.1% (IVS) |
| **FEASIBILITY STENT** | 16.8% | 8.7% | 22.7% (IVS) |

**Minor Deficiencies (FDA questions in italics)**

*#1) For the randomized cohort line listing...please include (the information with respect to previous surgery or de novo stenting), and stratify the analysis by de novo and post-endarterectomy subjects for those receiving a stent.*

The sponsor supplied the requested information. There were 127 patients with *de novo* stenosis, and 37 who had post-endarterectomy stenosis. Cumulative MAE at one year were 17/127=13.7% and 3/37=8.2%, respectively. The cohorts were also compared with respect to lesion success, procedure success, in-vessel and in-stent stenosis at 360 days, major and minor ipsilateral stroke at 360 days, and major bleeding. Though some of the numbers are small, there were no statistical differences between cohorts.

*#2) Please supply the same analysis as in #1 above to the cohort of feasibility subjects*

The sponsor supplied the requested data. There were 194 patients who received stents for *de novo* lesions, and 59 who received stents for post-endarterectomy lesions. MAE rates at 360 days for *de novo* and post-endarterectomy lesions were 21/194= 10.8% and 5/59=8.5%, respectively. As in the previous comparisons there were no statistical differences between groups with respect to death, major or minor ipsilateral strokes or bleeding complications at 360 days.

*#3) Please stratify patients with respect to anatomic versus co-morbid risk factors for both the pivotal and feasibility cohorts.*

The sponsor states that insufficient data for the requested analysis had been collected for the feasibility study.

The patients in the randomized arms were stratified by anatomic and medical (co-morbid) criteria. There were few statistical differences between group. When stratified anatomically, there were more patients with history of cardiac arrhythmias in the surgical group (8/35=22.9%) than in the stent arm (1/36=2.8%), p=0.01. There were more patients with previous CABG in the stent group (18/39=46.2%) than in the surgical group (8/35=22.9%), p=0.05. Of particular interest, there was no difference between arms with respect to previous CEA. When classified by medical high risk, there were no statistical differences between groups.

There were significant differences in MAE at 360 days when patients were stratified by anatomic and medical criteria. The anatomic high-risk patients had an MAE rate of 10.3% for stented patients, and 5.6% for CEA patients, whereas patients stratified by medical high risk co-morbidities had rates of 14.5% and 23.1% for stented and CEA patients, respectively. The differences were accounted for largely by a higher death and coronary atherosclerosis deaths.

*#4) Please provide an interpretation of the data collected on patients in the stent and CEA registries in terms of how they could be utilized to provide evidence for the safety and effectiveness of the stent relative to CEA.*

Only 7 patients were entered into the CEA arm of the registry. The sponsor states, with reason, that the number is too small for meaningful interpretation. The sponsor also states that the 406

patients in the stent arm of the registry "included those patients who met the criteria for SAPPHIRE, but were determined by the surgeon at each site to be at too high risk for carotid endarterectomy, and therefore inappropriate for randomization". The sponsor documents 5 clinical characteristics that were statistically more prevalent in the stent registry than in the randomized CEA cohort: angina class CC III or IV, prior CEA, Previous CEA with recurrent stenosis, history of stroke, and patients with 2 risk factors. The sponsor compared the MAE rate for this presumably higher risk group of patients (15.8%) with that of the randomized CEA cohort (19.2%) and found no statistical difference (p=0.33).

*#5) Adequate data should be provided for all stent models and sizes that you intend to market. The 5mm size was not represented in any cohort, and other sizes had minimal representation. Please provide data for this size.*

The sponsor provides data for all stent sizes. Of a total 896 stents implanted, only 4 were of 5mm. At the larger end, only 2 were 7-10mm tapered.

## Commentary

Primary Endpoint

The rate of MAE in stented patients at 360 days (12.2% +/-2.6) was lower than that of CEA (20.1% +/-3.4%), almost reaching statistical significance (p=0.053).

Secondary Endpoints

Initial failure to deliver the stent or difficulty in delivering or retrieving the protection device led to a high incidence (approximately 50%) of post procedure high-grade stenosis. The sponsor wanted to add the following clarification: Device success in the Sapphire protocol was defined as an achievement of <30% diameter stenosis by **angiography** post-revascularization procedure. For patients that had an initial failure to deliver the stent, or difficulty retrieving the protection device, the post procedure diameter stenosis was <30% in all but one patient (Patient 34 – Failed to deliver stent and converted to CEA). Regarding the comments from the Ultrasound Core lab that appear in the narratives for those patients: Peak systolic velocities are often mildly to moderately increased during the early post-revascularization period (prior to reaching hemodynamic baseline). Early in the conduct of the trial, those increases in velocity were interpreted as an increase in diameter stenosis. This was discovered as longer term follow up showed velocities in those same patients had stabilized. There were relatively few complications related to either the surgical or vascular access sites. There was a steady, but significant restenosis rate with time in both stent and CEA arms, though there was no significant difference between arms. Neurologic follow up was reasonably complete.

Response to Deficiencies

The sponsor has supplied data to one-year and two-year follow-up for the randomized arms, and for the stent registry arm. Three-year data was presented for the feasibility arm. Data for the CASCADE study was not available beyond one year. There were no differences between randomized stent and CEA arms with respect to MAE or restenosis at two years. Nevertheless,

the two-year MAE and ipsilateral stroke rates are substantial in both randomized arms, as well as the registry stent arm:

*Total In-Vessel Stenosis

For the Feasibility cohort, the 3-year MAE rate was 13.9% +/-2.9% or 21.8% +/-3.5%, depending on the censoring method (See Amendment #2, Dec. 30, 2003, p6.)

There are no statistically significant differences between compared groups. Even among those groups not directly compared there is a noticeable similarity.

With respect to comparisons between those patients receiving stent treatment for *de novo* versus post-CEA stenosis, there appear to be no significant differences in results with respect to death, major or minor ipsilateral stroke, or bleeding. This was true in both the randomized and feasibility cohorts.

Stratification of the randomized cohorts by anatomic versus medical high risk also demonstrated that stent implantation was not inferior to CEA, but those patients classified as high-risk by medical comorbidities had significantly greater rates of MAE in both randomized arms when compared with those patients classified by anatomic severity. There was a high percentage of asymptomatic patients in **all** groups (377/740 =51%). Of the patients receiving a stent in the randomized arm and in the registry, 331/573=58% were asymptomatic. In the registry alone over 2/3 of patients were asymptomatic (281/406=69%), yet the 30-day MAE event rate was 6.9%.

The sponsor employs OPC criteria derived from the NASCET trial (NEJM 1991; 325:445-453), but this study enrolled patients that were both symptomatic (neurologically: TIA or non-disabling stroke within 120 days) and had high-grade ipsilateral carotid stenosis (75-99%).

*Question #1: Please derive OPC hypothesis from ACAS study of CEA v. medical therapy in asymptomatic patients (JAMA 1995; 273:1421), or from the ECTS study severe stenosis cohort (Lancet 1991; 337: 1235-43) for comparison. FDA should clarify that the sponsor was not asked this question; we thought it would be best left up for discussion by the Panel, and if such analyses are deemed appropriate, we can ask for such an analysis.*

The number of stents implanted at the smallest and largest diameters is very small. Presumably, the larger diameter is not likely to present hemodynamic problems, but the smallest size (5mm) could be problematic.

*Question #2: Please submit such data that exist specifically for those patients who had 5mm stents implanted, specifically MAE and ultrasound at the specified time frames. In the absence of such data, please consider a PMA supplement when such data become available. FDA should clarify that we posed this question differently to the sponsor; we asked them to provide data for this size, or a justification for including this size. The sponsor responded that the 5mm stent was utilized in the registry and feasibility studies in 4 patients [4/896 (0.45%)]. In addition, the following points were presented as justification to consider this size:*

> *-Although the majority of patients required stents in the 6-8mm diameter range, other sizes provided treatment for varying patient anatomies and lesion locations.*

*-Reliability and PPQ testing demonstrates that 5mm stents are comparable to 8mm stents for radial and chronic outward force.*

*-PRECISE stents have similar open area, ranging from 82.5% to 89.5%, are constructed of identical material, and have minimal foreshortening (<10%). And, 5-8mm PRECISE stents have identical design.*

Statistician Memos (original PMA and amendments, plus answers to statistical questions)

**Introduction**

The devices under review are the PRECISE™ Nitinol Stent System, PRECISE™ RX Nitinol Stent System, ANGIOGUARD™ XP emboli capture guidewire, and ANGIOGUARD™ RX emboli capture guidewire, sponsored by Cordis Corporation. The clinical study (SAPPHIRE), conducted under IDE, has multiple components. It consists of a multicenter, prospective, randomized clinical trial, initially designed as a group sequential trial, in which patients are randomly assigned to treatment with carotid endarterectomy (control group) or the investigational device system PRECISE™ Nitinol Stent System with ANGIOGUARD™ XP emboli capture guidewire (treatment group). Additionally, it also consists of a "stent registry" and a "surgical registry". The "stent registry" is made up of patients enrolled in the clinical study who are considered as being too high-risk for carotid endarterectomy (CEA) and therefore not suitable for randomization. The "surgical registry" is made up of patients enrolled in the clinical study who are considered as being too high-risk for stenting and therefore not suitable for randomization. There are 334 randomized patients, 167 in the treatment group and 167 in the control group (8 patients in the treatment group and 16 patients in the control group did not receive the assigned treatment). The randomized clinical trial was conducted in such a way that the original group sequential protocol was neither followed (for reasons unclear to this reviewer) nor replaced by an alternative protocol. The sponsor asked that we amend our review memo to include the following: On March 26, 2004, Cordis provided FDA with a much more detailed description of why the group sequential analysis was not conducted and it has been explained by our expert consultants that a trial stopped for administrative reasons does not require an alternative analysis. However, we maintain that the decision not to follow the protocol was made much earlier than the decision to stop the trial, that these two issues are separate, and that we still do not understand the reason for not following the original sequential protocol. The trial was discontinued on June 11, 2002, due to "slow enrollment, the unwillingness of surgeons to refer patients, competing non-randomized trials, and waning physician interest in randomizing patients". There are 406 patients in the stent registry and 7 patients in the surgical registry. Cordis is not aware of any patients who turned down entry into the stent or surgical registries.

**Statistical Issues**

The clinical protocol specified two primary endpoints: 1) composite of major adverse clinical events including death, any stroke, and/or myocardial infarction at 30 days post procedure, and 2) the same 30 day composite of major adverse clinical events plus death and/or ipsilateral stroke between 31 days and 12 months post-procedure (copied from page 45, Volume 2 of the PMA). The sponsor asked that we provide the following clarification regarding their primary endpoints: It is acknowledged by Cordis that the study endpoint was unusual in that the components of the composite endpoint change over time. However, it is important that we do not confuse it as 2 endpoints. The study had one primary endpoint that consists of a composite of clinical events at 360 days. In the randomized clinical trial, the statistical hypothesis for the primary endpoints is formulated in terms of a parameter ?, defined by the quantity $f(t)=-\log(-\log(1-p_E(t)))+\log(-\log(1-p_C(t)))$, where $p_E(t)$ and $p_C(t)$ are the probabilities of an adverse event constituting the primary endpoints in the first t months in the treatment and control groups respectively. It is assumed that $f(1)=f(12)$, and the common value is denoted by ?. The clinical protocol specified

that if a 95% confidence interval (based on data from the randomized clinical trial) for ? includes only values greater than -0.240, then the investigational device system used for the treatment group can be declared as non-inferior to CEA (administered to the control group). The 95% confidence interval for ? reported in the PMA is [-0.03620, 1.05149], supporting the declaration of non-inferiority. The sponsor was requested to submit detailed computational steps for this confidence interval. Attached to this review memo is the document that the sponsor has submitted so far in response to FDA's request for detailed computational steps for the confidence interval for ?.

The randomized trial has at least two remarkable features in its design and conduct. With regard to the study design, it does not have a set of inclusion/exclusion criteria in the usual sense, in that patients enrolled in the study are subjectively selected into the randomized trial. Consequently, the patient population of which the randomized clinical trial is representative may not have a precise, objective, and consistent definition. With regard to the study implementation, the original group sequential protocol was neither followed nor replaced with an alternative protocol. On both features the sponsor was requested to provide comments. The sponsor's comments are summarized below.

The sponsor agreed that the population used for the randomized trial may not have a precise definition, and proposed to address this issue in the summary of safety and effectiveness (SSE) by describing the distributions of high-risk factors, demographic variables, and lesion characteristics for the randomized and registry patients. At the same time, the sponsor also argued that the results of the randomized study may be generalized to a broad population, by claiming that many high-risk factors have similar distributions among the randomized and stent registry patients, that the treatment effect seems not to depend on some of the high-risk factors, and that the event rate constituting the primary endpoint is similar in the randomized stent arm and the stent registry.

The sponsor does not consider the deviation from the initial group sequential protocol to be a problem for the randomized trial. In particular, the sponsor argued that the statistical inference can be conducted for the randomized trial as though it had had a protocol that had pre-specified the sample size to be 334 (167 per treatment arm), the sample size at which the trial was discontinued. A justification given by the sponsor for this approach is that no interim analyses had been performed (following the original group sequential protocol).

In the original PMA submission the sponsor made a straightforward comparison between the outcomes of the patients in the stent registry and those randomized to CEA. In the initial FDA deficiency letter for the original PMA it was pointed out that such straightforward comparisons are not meaningful and do not constitute an interpretation of data; in particular, they cannot be used directly as evidence for the safety and effectiveness of the investigational stent system relative to CEA. In response, the sponsor stated that there are several risk factors that are more prevalent in the stent registry than in the randomized CEA arm, and still the primary endpoint of the rate of major adverse events at 12 months is not significantly different between the stent registry (15.8%) and the randomized CEA arm (19.2%). The sponsor stated: "We believe that this comparison can be utilized to provide evidence for the safety and effectiveness of the stent relative to CEA".

At this point, FDA reminded the sponsor that comparing the stent registry with the randomized CEA arm is an instance of observational study. For a comparison to be acceptable as evidence, at least an observational study using appropriate methods needs to be completed. In response, the sponsor

proposed to conduct a propensity score analysis on the groups of stent registry and randomized CEA arm. Upon receiving this proposal, FDA made a few comments with regard to some options and opportunities for the sponsor to consider. The FDA pointed out that the propensity score analysis may be applied to the stent registry and the entire group of randomized patients, since it was not obvious that the sponsor had considered this option. The FDA brought to the sponsor's attention that the fact that the entire group of randomized patients was randomly divided into the stent and the CEA arms may be taken advantage of to enrich the results of the proposed propensity score analysis. The FDA also mentioned the opportunity for the sponsor to use the results of the propensity score analysis to address the issue of generalizing the results of the randomized trial to an objectively defined population. Currently the response to those suggestions has not been submitted to this reviewer.

The analysis planned in the original protocol for the stent registry is the comparison of the rate of major adverse events consisting of death, any stroke and/or MI on the first 30 days and death or ipsilateral stroke to 12 months post-procedure to an objective performance criterion (OPC). The null hypothesis is the above event rate being no lower than the OPC plus a margin (d) of 4%. Non-inferiority to OPC can be declared upon rejection of the null hypothesis. The OPC was chosen to be 15% for patients with co-morbidities and 11% for patients with unfavorable anatomic conditions. The overall OPC, which is the weighted average of the above two values, is 12.94% for the stent registry. With an observed event rate of 15.8%, the null hypothesis is not rejected (p=0.2899), and hence non-inferiority to OPC cannot be declared.

**Statistical Reviewer's Main Concerns**

?? The randomized study was originally designed as a group sequential clinical trial, but the group sequential protocol was not followed and an alternative protocol had not been developed. To what extent would the statistical inference involving the results of the randomized study be affected by the fact that the original group sequential protocol was neither followed nor replaced by an alternative protocol?

?? Has the sponsor made attempts to address the issue of generalizing the results of the randomized trial to an objectively defined population through valid analyses of the SAPPHIRE trial data, and to what extent are those attempts successful?

**APPENDIX: The sponsor's response to the request to submit detailed computational steps for the confidence interval for ?**

**Calculation of a point estimate and confidence interval for the treatment effect following observation of interval-censored survival data**

The primary analysis has focused on the incidence of major adverse events, including death, stroke, or myocardial infarction within either one month or one year. The one-month and one-year adverse event rates are combined by considering the data as interval-censored survival data, with the number of patients experiencing adverse events after one month and at the end of one year being recorded. In the analysis, the time of the event is set to be one month for all events

occurring within the first month and one year for all events occurring within months 2 to 12. Patients who do not have an event within the first year are considered censored at 12 months.

If we denoting by $p_E(t)$ and $p_C(t)$ the probability of an event in the first $t$ months on the experimental and control treatments respectively, a measure of the treatment efficacy up to time $t$ is

$$? (t) = ? \log(? \log(1 ? p_E(t))) + \log(? \log(1 ? p_C(t))) \qquad (1)$$

for t equal to 1 and 12. The statistical model assumes that this treatment difference is equal at times 1 and 12. The common value, which will be denoted by ?, is therefore a measure of the overall treatment difference.

If the hazards of adverse events on the experimental and control arms are proportional, the quantity ? (t) is constant over time, with exp(–? (t)) equal to the hazard ratio. The assumption that ? (1) = ? (12) is, however, considerably less restrictive than the assumption of proportional hazards.

A method for the calculation of a point estimate and confidence interval for ? is described by Whitehead (see Whitehead and Thomas, 1997, and Whitehead, 1997, Section 3.5). This is based on the calculation of the efficient score and observed Fisher's information for ?, which will be denoted by Z and V respectively.

Suppose that $n_{1E}$ and $n_{1C}$ are the numbers of patients in the experimental and control groups respectively for whom one-month data are available, with $n_1 = n_{1E} + n_{1C}$, and $n_{2E}$ and $n_{2C}$ are the numbers of patients in the experimental and control groups who did not experience an adverse event during the first month and for whom 12 month data are available, with $n_2 = n_{2E} + n_{2C}$. Using similar notation, let $f_{1E}$, $f_{1C}$, $f_{2E}$ and $f_{2C}$ denote the numbers of one-month and 12-month adverse events in the experimental and control groups, with $f_1 = f_{1E} + f_{1C}$ and $f_2 = f_{2E} + f_{2C}$. The test statistics Z and V are then given by

$$Z = q_1 ( n_{1E} f_{1C} – n_{1C} f_{1E})/n_1 + q_2 ( n_{2E} f_{2C} – n_{2C} f_{2E})/n_2 \qquad (2)$$

*and*

$$V = q_1^2 (n_1 – f_1) n_{1E} n_{1C} / n_1 f_1 + q_2^2 (n_2 – f_2) n_{2E} n_{2C} / n_2 f_2 \qquad (3)$$

*where* $q_i = –log(1 – f_i/n_i)$ *for* $i = 1,2$.

For small values of ? and a large sample size, Z is normally distributed with mean ?V and variance V (see Scharfstein, Tsiatis and Robins, 1997). An approximate maximum likelihood estimate of ? is thus given by

$$\hat{?} = Z/V. \qquad (4)$$

Since, conditional on the observed value of V, this estimate is asymptotically normally distributed with variance 1/V, an approximate confidence interval is given by

$$(\hat{\theta} - 1.96/\sqrt{V}, \hat{\theta} + 1.96/\sqrt{V}). \qquad (5)$$

It is the confidence interval (5) that has been reported, and on which the non-inferiority claim is based.

***References***

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